

Immunotherapy-related hepatitis: real-world experience from a tertiary centre

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Abstract

Objective: Immune Checkpoint inhibitors like anti-PD-1 drugs Nivolumab and Pembrolizumab and anti-CTLA-4 drug Ipilimumab have become standard of care in many metastatic cancers. Immunotherapy-related hepatitis and cholangitis present a diagnostic and management challenge, being rare and incompletely characterized. We aim to report the incidence, features and treatments used for this in a real-world setting and to identify useful biomarkers, which can be used to predict effective use of steroids

Design: Retrospective review of 453 patients started on immunotherapy over 7 years

Setting: Tertiary hepatology and oncology centre

Patients: 21 patients identified with immunotherapy-related hepatotoxicity

Results: Hepatitis was most common in those receiving dual therapy (incidence 20%), with 75% of Grade 4 hepatitis cases occurring with ipilimumab-containing regimens. Corticosteroid monotherapy is first line treatment, but doses above 60mg OD prednisolone do not demonstrate any additional benefit in time to hepatitis resolution. The ALT reduction in steroid-responsive hepatitis is typically rapid (with a halving of ALT within 11 days). The commencement of additional immunosuppression (typically mycophenolate) appears safe and prompts a more rapid fall in ALT than corticosteroid use alone. Infliximab was safely used twice as hepatitis treatment. We also describe one patient with rare immunotherapy-induced biliary disease.

Conclusions: Vigilance is required for detection of immunotherapy-associated liver disease as, other than dual immunotherapy, we can identify no predictive factors for its development. Our data suggest corticosteroid response is not dependent on the higher dosing regimens. Early escalation of immunosuppression may be of benefit in the absence of a rapid response to corticosteroids.

Keywords

Checkpoint inhibitor; Hepatitis; Immunotherapy; Drug-induced liver injury

Summary Box

What is already known about this subject?

- Immune-checkpoint inhibitor therapy results in a variety of autoimmune reactions affecting different organs including the liver
- There is no significant difference in survival between those patients who developed ICPI hepatitis and those who did not
- Corticosteroids are the first line treatment for immunotherapy-related hepatitis

What are the new findings?

- Treatment escalation should be to an additional steroid sparing agent rather than an increased dose of steroid if the ALT does not respond rapidly as higher doses are not more effective
- There are no clear clinical biomarkers predicting who will require steroid sparing agents in addition to steroid therapy for hepatitis.
- There are two potential groups of non-responders – those who develop a clear failure of therapy with a ‘rapid ALT rise’ hepatitis and those where the ALT shows a more delayed rise, with no immediate response to starting therapy
- Although Liver irAE usually manifests as a hepatitis, it can also manifest in a predominant biliary pattern

How might it impact on clinical practice in the foreseeable future?

- Consider escalation of treatment early in cases where the ALT does not recover within a few days though this strategy needs to be validated in larger numbers of patients
- Patients can be re-challenged with another type of immunotherapy without getting further hepatotoxicity

Background

Immune checkpoint inhibitors (ICPIs) represent a novel class of oncological therapy that increase survival in patients with various tumours. These revive exhausted immune populations that then react against cancer cells through blocking physiological anergic pathways involving the Programmed Death 1 (PD-1) and Cytotoxic T-Lymphocyte Associated (CTLA) proteins. Whilst ICPIs are known to deliver durable responses and are being trialled in an expanding number of cancer types (1–10) there is caution in their use because of immune-related adverse events (irAEs) that can affect multiple different organ systems (11).

Liver irAEs are uncommon and vary in severity from mild to life-threatening. Reports suggest the predominant histological pattern of liver injury is a pan-lobular hepatitis resembling autoimmune hepatitis (12–14) and more rarely, fibrin ring granulomas (15). The factors predisposing to liver irAEs and whether pre-existing liver conditions confer an increased risk for irAEs are unknown. Furthermore, many clinical trials excluded patients with such conditions and/or organ dysfunction (16). There are reports of immunotherapy use in patients with viral hepatitis (17) and recent evidence suggests that both anti-CTLA-4 (18) and anti-PD-1 (19) monotherapy respectively can be safely administered to patients with pre-existing autoimmune disease without increased severe toxicities (20). The Food and Drug Administration (FDA) and American Society of Clinical Oncology (ASCO) have championed the expansion of clinical trial eligibility criteria, which may aid in the characterisation of the safety of immunotherapies in these patients with pre-existing liver disease (21,22).

We present a cohort of patients identified to have liver irAEs.

Methods

453 patients started checkpoint inhibitor therapy at a single tertiary centre between December 2011 and June 2018. Electronic patient records and oncology databases were retrospectively analysed for clinical data on two occasions by separate teams. Analysis was conducted using GraphPad PRISM™ and IBM SPSS™ software. Type and number of cycles of immunotherapy, cancer type, survival, biochemistries and treatment received were recorded for all patients with liver irAEs. Checkpoint-inhibitor-associated liver disease was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5 (23). The choice of therapy, threshold for starting and of escalation varied by clinical context but was in line with national and local guidelines (Supplementary File 3). Briefly, if hepatitis was more severe than Grade 1, intravenous methylprednisolone or oral prednisolone was commenced, followed by escalation to steroid sparing agents (SSAs) such as mycophenolate mofetil (MMF) (in 1g BD or 500mg BD doses), Tacrolimus, or Infliximab (5mg/kg) if necessary. Treatment failures represent disease courses where therapy for ALT control was unsuccessful as assessed at 7 days. Treatment failure 'Rapid Risers' were defined as those where the ALT rose within 7 days, and 'Slow risers' as those where the ALT remained stable despite initiating treatment.

Results

In total, 21 patients with liver irAEs and their clinical features are shown in Table 1. 20 patients were categorized as having developed checkpoint inhibitor-associated hepatitis, an incidence of 4% which is comparable to published literature (24,25). One patient developed biliary

pathology (Identifier, _272). Two further patients with abnormal LFTs were excluded from analysis - one had underlying Hepatitis C infection, and the other was a trial patient who remained blinded to checkpoint inhibitors versus placebo.

Patients received various regimens, including monotherapy and dual therapy with both CTLA-4 and PD-1 inhibitors. One patient developed hepatitis separately on both anti-CTLA-4 (Ipilimumab) and anti-PD-1 (Pembrolizumab) therapy (Identifier: _07).

17 patients had ICPI treatment for melanoma, two for Lung Cancer (Identifiers _272, _896), and one each for Renal cell cancer (Identifier:_42) and Epithelial Mesothelioma (Identifier:_92). In 12 patients, checkpoint inhibitors were given as first-line systemic therapy, in 6 patients, it was second line therapy (previous Premetrexed, Dabrafenib, Carboplatin, Bevacizumab or PAN-RAF inhibitor) and in 2, it was third line therapy (previous Dabrafenib-Trametinib or Sunitinib-Cabozantinib). The remaining patient had received hormone therapy for breast cancer (Letrozole). No patient had prior autoimmune disease.

Patient ID	Age	Sex	Cancer	Regimen	Pathology	Peak ALT	Treatment	Other Autoimmune effects
I1(_08)	72	M	Melanoma	Pem then Ipi(H)	Hepatitis	706	Prednisolone	Colitis
I+N1(_38)	67	M	Melanoma	Ipi and Niv together(H)	Hepatitis	73	Methylprednisolone, Prednisolone, Infiximab	Colitis, Rash, Hypoadrenalism
I2, P1(_07)	76	F	Melanoma	Ipi (H), then Pem (H)	Hepatitis	122(I), 699(P)	Prednisolone, MMF, Tacrolimus	Colitis
I+N2(_72)	63	M	Melanoma	Ipi and Niv together(H)	Hepatitis	88	Prednisolone	Colitis, Rash
I+N3(_40)	70	M	Melanoma	Ipi and Niv together(H)	Hepatitis	434	Prednisolone	Colitis
I3(_87)	42	M	Melanoma	Pem then Ipi(H)	Hepatitis	1932	Dexamethasone, Prednisolone, MMF	
I+N4(_59)	43	F	Melanoma	Ipi and Niv together(H)	Hepatitis	152	Prednisolone	Rash
I+N5(_83)	46	M	Melanoma	Ipi and Niv together(H)	Hepatitis	834	Prednisolone, MMF	
I4(_038)	65	F	Melanoma	Ipi only (H)	Hepatitis	1635	Prednisolone	
N1(_42)	71	M	Renal Cell	Niv only (H)	Hepatitis	102	No treatment	
P2(_91)	61	M	Melanoma	Pem only (H)	Hepatitis	824	Methylprednisolone, Prednisolone	
I+N6(_17)	49	F	Melanoma	Ipi and Niv together(H)	Hepatitis	2854	Methylprednisolone, Prednisolone, MMF, Infiximab	
I+N7(_002)	45	F	Melanoma	Ipi and Niv together(H)	Hepatitis	610	Prednisolone, MMF	Rash, Hypoadrenalism, Hypothyroidism, Type 1 Diabetes, Mucositis
I+N8(_44)	51	M	Melanoma	Ipi and Niv together(H)	Hepatitis	790	Methylprednisolone, Prednisolone, MMF	
I+N9(_834)	21	F	Melanoma	Ipi and Niv together(H)	Hepatitis	422	Methylprednisolone, Prednisolone, MMF	Gastritis, Pancreatitis
P3(_92)	73	M	Epithelial Mesothelioma	Pem only (H)	Hepatitis	1377	Methylprednisolone, Prednisolone	
CHKMT238(_97)	71	F	Melanoma	Blinded Niv/Ipi (H)	Hepatitis	299	Prednisolone, MMF	
I+N10(_58)	37	F	Melanoma	Ipi and Niv together(H)	Hepatitis	214	Prednisolone	Rash, Hyperthyroidism
P4(_272)	75	F	Non-small cell Lung	Pem only (C)	Cholangitis	444	Prednisolone, Ursodeoxycholic acid	
P6(_896)	69	M	Non-small cell Lung	Pem only (H)	Hepatitis	132	No treatment	Pruritis, Thyrotoxicosis
I+N16(_077)	29	M	Melanoma	Ipi and Niv together(H)	Hepatitis	1343	Methylprednisolone, Prednisolone	

Table 1. Clinical data for all patients who had abnormal liver function tests I, Ipi = Ipilimumab (anti-CTLA-4), P, Pem = Pembrolizumab (Anti-PD-1 Antibody), Niv = Nivolumab (Anti-PD-1 Antibody) CHKMT238 = Checkmate238 Trial of Ipi vs Niv (Blinded). MMF = Mycophenolate Mofetil. (H) indicates which agent patient was on when they developed hepatitis. (C) indicates patient developed cholangiopathy. Patient IDs are indicative of which regimen patients were on when they developed colitis.

Clinical Outcomes

The median follow-up time for patients in the hepatitis cohort was 456 days (Range 46-1710) and mean 524 days. Hepatitis was most common for patients who received simultaneous dual therapy (20%, Figure 1(a), Table 2), mirroring trends in ICPI colitis (26).

In line with previous published series There was a trend towards, but no significant difference in survival between those patients who developed ICPI hepatitis and those who did not (Figure 1(b)). (27,28),

All hepatitis patients were diagnosed and managed empirically without liver biopsy. ALT was the most consistently measured and sensitive biomarker (Figure 1(c)). Bilirubin, ALP and Albumin underwent smaller fluctuations (Supplementary File 1(a-c)), whereas the PT and INR did not change (not shown).

Treatment Response

ICPI hepatitis was treated with steroid induction (18/20 patients, the remaining patients had grade 1 hepatitis). Immunotherapy was withheld until the ALT normalized.

Clinical feature	Ipilimumab	Nivolumab	Pembrolizumab	Checkmate 238	Ipi+Niv (Simultaneous)	Total
Instances of hepatitis	4	1	4	1	11	21
Onset of hepatitis after treatment (days) (Median, range)	36 (30-62)	85	31.5 (14-103)	29	39 (6-90)	38.5 (6-103) Average: 44
Age at time of hepatitis (years) (Median, range)	68.5 (42-76)	71	71 (61-76)	71	46 (21-70)	62 (21-76) Average: 56
Number of Males (%)	2 (50%)	1 (100%)	2 (50%)	0	6 (54%)	11 (52%)
Clinical Properties broken down by treatment group						
Grade 1 (n, %)	1 (100%)		2 (18%)		3	
Grade 2 (n, %)	1 (25%)		2 (18%)		4	
Grade 3 (n, %)	1 (25%)		5 (45%)		9	
Grade 4 (n, %)	2 (50%)		2 (18%)		5	
Number of patients needing hospital admissions for hepatitis	3 (75%)		7 (60%)		13 (62%)	
Number of patients having liver biopsy	0	0	0	0	0	0
Treatment						
Steroids only (n)	4	0	2	5	11 (52%)	
Infliximab (n)	0	0	0	2 (1 for Colitis)	2	
Mycophenolate mofetil (n)	1	0	1	5	8	
Tacrolimus (n)	0	0	1		1	

Table 2. Clinical features and management outcomes of ICPI hepatitis. Breakdown by type of regimen patients were receiving at the time of development of hepatitis, as well as clinical outcomes.

Treatment Successes

All patients were managed in line with national and local guidelines. We subdivided patients depending on whether the hepatitis responded to steroid monotherapy (typically IV Methylprednisolone followed by PO Prednisolone or PO prednisolone alone) or required the addition of Steroid sparing agents (SSAs) if monotherapy failed by day 7. There was no link between clinical characteristics such as patient gender or immunotherapy regimen with the requirement for SSAs plus steroids versus steroids alone (Supplementary File 2).

The aggregate trends for the fall in ALT (Figure 2(a), individual trends in Supplementary File 1) show a slower drop in ALT for those treated with steroid monotherapy as compared to those treated with a second immunosuppressive agent, despite a higher ALT at SSA initiation. This suggests that addition of a second immunosuppressive agent accelerates time to resolution, with no adverse effect on survival (Supplementary File 2(i)).

Notably, 2 patients in this cohort received Infliximab – one for treatment of ICPI hepatitis, and one for ICPI colitis (whilst having no hepatitis at the time of the colitis). In one case, there was clear improvement (Figure 1(d)). In the other, the ALT was measured for 112 days after the drug was administered and remained normal, i.e. no medication-induced hepatotoxicity was seen.

Treatment Failures

All ALT trends in individual hepatitis flares which initially failed control therapy, are shown in Figure 2(c). Despite small numbers, a supervised clustering approach delineated two potential patterns. In the first week after escalating immunosuppression for hepatitis, the cohort of “rapid risers” had an ALT rise of 100 IU/L per day, whereas the “slow risers” showed either no

response to treatment or an increase in ALT by an average of 5 IU/L per day. Although all 'slow risers' were initially on steroid monotherapy only, two of the three only responded after the addition of 2 SSAs, specifically MMF and either Tacrolimus or Infliximab.

Effect of Steroid Doses

The data was analysed for the effect of steroid doses within the successful steroid-only cohort. Two broad categories were identified – patients treated with a 'lower dose' regimen of 50-60mg Prednisolone, and those treated with a higher 1mg/kg daily dose.

A higher prednisolone dose did not shorten the time to ALT normalization (Figure 2(b)), despite the aggregate ALT being higher at baseline in patients treated with a lower prednisolone dose. The data appear to show no clear benefit to using a higher steroid dose.

Re-challenge with immunotherapy

Four patients with ICPI hepatitis were given further immunotherapy after resolution of Liver function tests. Patients I+N5(_83) and I+N4(_59) who both developed combination immunotherapy associated hepatotoxicity were given maintenance nivolumab and they have had 8 and 19 cycles respectively without hepatotoxicity so far. Patients I+N2(_72) and I+N9(_834) were given second line Pembrolizumab after hepatotoxicity with combination immunotherapy and have tolerated 10 and 2 cycles respectively to date.

ICPI Cholangiopathy

One patient developed a predominantly cholestatic pathology on ICPI (Table 1, Figure 1(e)). The elevation in ALP was markedly more than in ICPI hepatitis, whereas the rise in ALT was more modest. The trends for Bilirubin and Albumin were similar.

Late peaks of ALP in the time course of the treatment were due to re-introduction of ICPI drugs, with resolution occurring on administration of oral steroids. The patient underwent a magnetic resonance cholangiopancreatogram as well as a liver biopsy. These demonstrated bilobar intrahepatic bile duct stricturing and ectasia, and portal based mixed inflammation with minimal lobulitis. The cholestasis was responsive both to steroids and ursodeoxycholic acid. Taken together, this indicated a pathology driven by immune checkpoint blockade.

Discussion

This series reports the incidence, clinical features and treatments used for liver irAEs, but also attempts to identify useful biomarkers and how they can be used to predict effective use of steroids.

Immune-checkpoint inhibitor therapy results in a variety of autoimmune reactions – ranging from encephalitis (B cell mediated) to colitis (T cell mediated). There is variation both in terms of organ systems affected over time, as well as the intensity of an inflammatory response with repeat dosing. In addition, the autoimmune reaction, once initiated, does not consistently resolve on withdrawal of the drug, so may require longer term immunosuppression.

ICPI hepatitis is an uncommon side-effect (29), which despite inter-individual variability, displays distinct histological characteristics to autoimmune hepatitis or drug-induced liver injury (30,31). In this cohort of 21 patients, novel trends can be identified regarding the biochemical patterns of disease.

Although there are as yet no defined predictive factors for developing hepatitis, it appears to be commonest in the cohort receiving simultaneous PD-1 and CTLA-4 blockade. 75% (n=3) of

instances of Grade 4 hepatitis were in Ipilimumab-containing regimens. Our data suggests that all patients develop hepatitis within 120 days of starting checkpoint therapy, which could be timed with immunotherapy cycles delivered every 2-3 weeks to check for hepatitis onset.

Within the steroid only treatment cohort, the ALT fell below the treatment threshold of Grade 2 hepatitis (ALT 112) within 20 days in all patient courses except for four - I3, I4, I+N7 and I+N9 (Supplementary File 1(d)). Increased patient numbers are required to verify these trends, but this may represent a cohort of patients that would benefit from escalation of therapy earlier.

In the 9 instances where SSAs were employed, the ALT trends over time clustered together irrespective of regimens used, with similar slopes of response times (values falling to half of baseline ALT by 11 days).

The relevance of two patterns of non-response is unclear but may reflect immunological differences as no clinical factors differed between the cohorts.

Although patient numbers are small, data from this cohort suggests that the smaller 50-60mg OD Prednisolone dose is likely to be sufficient. Treatment escalation should be to an additional SSA rather than an increased dose of steroid if the ALT does not respond rapidly. This may reduce the incidence and/or severity of corticosteroid-related adverse effects in such patients.

Finally, no adverse events were noted with Infliximab use. Some guidelines advocate avoiding infliximab in immune-mediated hepatitis owing to the risk of liver failure (although they concede the evidence for this is lacking) (32). Other therapies such as anti-thymocyte globulin,

tacrolimus methotrexate, leflunomide and ciclosporin have also been reported to ameliorate immunotherapy-related hepatitis in cases that are steroid-refractory (33–36).

We describe one case of a predominantly cholangiopathic pathology that was responsive to steroids and ursodeoxycholic acid.

Abnormal liver biochemistry also occurs in this group of patients due to other causes of liver disease, such as viral hepatitis or sepsis. Liver screens and if necessary, biopsies, should form a key step in the investigation of abnormal blood tests in this cohort of patients (37).

Future work should seek to characterize this patient population in more detail. Early and routine liver biopsy, with flow-cytometry or single-cell RNA analysis may be helpful so that this heterogenous patient group may be better phenotyped. Clinical parameters are insufficient for predicting outcome (Supplementary File. 2), and we require peripheral biomarkers that can predict treatment response more accurately.

Conclusion

Incidence of liver irAEs was 4% in this cohort with ICPI hepatitis occurring within 120 days of the first dose of checkpoint therapy. A subset of patients did not respond to initial therapy with corticosteroids, and additional immunosuppression appears safe and effective. Corticosteroid doses above prednisolone 60mg daily were not associated with more rapid resolution of liver biochemistry.

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Figure Legends

Figure 1(a): Incidence of hepatitis and colitis in a 2011-2018 single tertiary centre cohort of patients receiving different treatment regimens. Combination therapy represented separately to single therapy. Demonstrates highest incidence in those receiving simultaneous PD-1 (Nivolumab) and CTLA-4 (Ipilimumab) therapy. Figure 1(b): Survival after initiation of ICPI therapy in this cohort of patients compared to patients who did not develop ICPI hepatitis or colitis. Trends towards improved survival if develop hepatitis, but not significant. Figure 1(c): Individual and aggregate (Lowess) trends in ALT (liver inflammation biomarker) after initiation of ICPI therapy for all patients with ICPI hepatitis. Fig 1(d): ALT trends in a single patient after initiation of ICPI therapy. Distinct patterns of response to different drugs, with inflammation not responding to addition of steroids or mycophenolate mofetil (MMF) but responding to a single dose of Infliximab. Fig 1(e): ALP (cholestasis biomarker) in a single patient with ICPI Cholangiopathy, as well as response to steroids and Ursodeoxycholic acid (UDC). I = Ipilimumab, I+N = Ipi + Nivolumab, N = Nivolumab, P = Pembrolizumab. CHKMT238 = Blinded to receive either Ipilimumab or Nivolumab. Suffixes (_08, _17 etc) represent individual patient codes

Figure 2(a): Lowess curves (aggregate ALT trends) comparing 3 ICPI hepatitis groups – episodes treated with steroids alone, those with steroids as well as steroid sparing agents (SSA) and those receiving no therapy. The rate of decrease of ALT with the addition of a SSA is significantly faster to steroid monotherapy. Fig 2(b) : ICPI Hepatitis ALT trends in response to treatment with two different doses of steroids. Lowess curves (aggregate ALTs) represented for each cohort. Using a higher dose of prednisolone (1mg/kg) does not accelerate the rate of fall of ALT, and instead shows that response may be slower, despite a lower starting aggregate ALT. Fig 2(c) : Individual ALT trends (dotted lines) in all ICPI Hepatitis episodes that failed initial immunosuppressive therapy. Supervised clustering of individual trends reveals two patterns of ALT rise, “Fast” and “Slow”, with the Lowess curves (aggregate ALT) for each represented. Individual ALT trends colour coded by whether they fell into the “Fast” or “Slow” category. I = Ipilimumab, N = Nivolumab, P = Pembrolizumab, I+N = Simultaneous Ipilimumab and Nivolumab therapy, CHKMT238 = Blinded Ipi vs Niv. MMF = Mycophenolate mofetil. IFX = Infliximab. Suffix (_08, _07) etc = individual patient codes.

Supplementary File 1(a-c) Individual and aggregate (Lowess) trends in Alkaline Phosphatase (ALP) (a), Bilirubin (b) and Albumin (c) after initiation of ICPI therapy for all patients with ICPI Hepatitis. Supp Fig 1(d) Individual ALT trends after initiation of immunosuppression in every patient responsive to steroid monotherapy alone (colour coded by regimen). Supp Fig 1(e): Individual ALT trends after initiation of immunosuppression in every patient requiring Steroid sparing agents (SSAs) added to steroid therapy for ICPI Hepatitis (colour coded by regimen). I = Ipilimumab, N = Nivolumab, P = Pembrolizumab, I+N = Simultaneous Ipilimumab and Nivolumab therapy,

CHKMT238 = Blinded Ipi vs Niv. MMF = Mycophenolate mofetil. IFX = Infliximab. Suffix (_08, _07) etc = individual patient codes.

Supplementary File 2(a) Interval between starting steroids and steroid-sparing agents (SSAs) in all cases of ICPI hepatitis, with considerable variation, but a median interval of 6 days, which is in line with clinical guidelines for escalation. Sup Fig 2(b)-(h): Clinical parameters are not useful in predicting which patients with ICPI Hepatitis will require steroids versus steroids and SSAs. Patient Gender (b), Age of patient at time of starting Immunotherapy (c), Presence of any immune-related adverse event, such as fatigue or thyroiditis (d), Presence of co-existent or prior colitis (e), Presence of co-existent or prior skin rash (f), Whether the patient received Chemotherapy prior to use of immunotherapy (g) and Type of Checkpoint therapy (h) all not significant. Analyses done using IBM SPSS software, with a multinomial logistical regression analysis and chi-squared test used. Sup Figure 2(i): There was no difference in survival between those patients requiring additional immunosuppression with SSAs versus those immunosuppressed with steroids alone. Analysis done using Graphpad PRISM software.

Supplementary File 3. Local Thames Valley guidelines on management of Immune checkpoint associated Hepatitis.